Summary of Product Characteristics

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT:

PANTOP-D[Pantoprazole Sodium Sesquihydrate and Domperidone Capsules 20/10 mg]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION :

Each capsule contains:

Pantoprazole Sodium Sesquihydrate USP

Equivalent to Pantoprazole 20 mg

(in the form of enteric coated pellets)

Domperidone BP 10 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM:

CAPSULE

Hard gelatin capsule of size '1' with Blue cap & Buff yellow coloured body, contains white coloured circular, biconvex, enteric coated pellet of Pantoprazole and white to off white freely flowing powder.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

Gastroesophageal Reflux Disease (GERD).

4.2 Posology and method of administration:

One capsule once daily or as directed by the Physician.

4.3 Contraindications:

This combination is contraindicated in patients with known hypersensitivity to Pantoprazole, substituted benzimidazole, Domperidone or to any component of the formulation.

4.3 Contraindications:{CONTD}

It should not be used whenever stimulation of gastric motility is to be avoided or could be harmful, eg. in the presence of gastro-intestinal haemorrhage, obstruction or perforation.

It is also contra-indicated in patients with

- Prolactin-releasing pituitary tumour (prolactinema).

•Co-administration with oral ketoconazole, erythromycin, or other potent CYP3A4 inhibitors, which prolong the QTc interval such as fluconazole, voriconazole, clarithromycin, amiodarone and telithromycin.

•Whenever stimulation of gastric motility might be dangerous, e.g. in the presence of gastro- intestinal haemorrhage, mechanical obstruction or perforation.

•In patients with moderate or severe hepatic impairment.

4.4 Special warnings and special precautions for use:

PRECAUTIONS:

PANTOPRAZOLE:

General:

Concurrent Gastric Malignancy: Symptomatic response to therapy with Pantoprazole does not preclude the presence of gastric malignancy.

Owing to the chronic nature of erosive esophagitis, there may be a potential for prolonged administration of Pantoprazole. In long-term rodent studies, Pantoprazole was carcinogenic and caused rare types of gastrointestinal tumors. The relevance of these findings to tumor development in humans is unknown.

Cyanocobalamin (Vitamin B12) Deficiency: Generally, daily treatment with any acid-suppressing medications over a long period of time (eg, longer than 3 years) may lead to malabsorption of cyanocobalamin (Vitamin B-12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been

4.4 Special warnings and special precautions for use:{CONTD}

PRECAUTIONS:

reported in the literature. This possibility should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.

Atrophic Gastritis: Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with Pantoprazole, particularly in patients who were H. pylori positive.

Bone Fracture: Several published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who

received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines.

Hypomagnesemia: Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically.

Tumorigenicity: Due to the chronic nature of GERD, there may be a potential for prolonged administration of Pantoprazole. In long-term rodent studies, Pantoprazole was carcinogenic and caused rare types of gastrointestinal tumors. The relevance of these findings to tumor development in humans is unknown.

4.4 Special warnings and special precautions for use:

PRECAUTIONS:

DOMPERIDONE:

Cardiac effects: An increase in the risk of sudden cardiac death or serious ventricular arrhythmias has been reported in some epidemiology studies. The risk may be higher in patients older than 60 years or at total daily doses more than 30 mg. In addition, there have been spontaneous reports of QTc prolongation, ventricular arrhythmias and sudden cardiac death in the post-market surveillance setting. Domperidone should be used at the lowest effective dose.

Prolactin levels: There are limited safety data in long-term use (i.e. beyond six months) of Domperidone. However, it has been shown to produce an increase in plasma prolactin. The raised level persists with chronic administration but falls to normal on discontinuing the drug.

Endocrine disturbances such as galactorrhoea, amenorrhoea, gynaecomastia and impotence have been reported with drugs which stimulate prolactin release. The clinical significance of elevated serum prolactin levels is unknown for most patients.

An increase in mammary neoplasms has been found in rodents after chronic administration of Domperidone and other prolactin stimulating drugs. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of these drugs and mammary tumorigenesis.

Domperidone does not affect plasma growth hormone or aldosterone.

Despite the lack of penetration of the blood-brain barrier, the possibility that extrapyramidal symptoms may occur in very rare instances after long-term use of Domperidone, should be considered.

4.5 Interaction with other FPPs and other forms of interaction:

PANTOPRAZOLE:

It is metabolized through the cytochrome P450 system, primarily the CYP2C19 and to a minor extent the CYP3A4 isozymes, and subsequently undergoes Phase II conjugation. Based on studies evaluating possible interactions of Pantoprazole with other drugs, no dosage adjustment is needed with concomitant use of the following: theophylline, cisapride, antipyrine, caffeine, carbamazepine, diazepam (and its active metabolite, desmethyldiazepam), diclofenac, naproxen, piroxicam, digoxin, ethanol, glyburide, an oral contraceptive (levonorgestrel/ethinyl estradiol), metoprolol, nifedipine, phenytoin, warfarin, midazolam, clarithromycin, metronidazole, or amoxicillin. [Clinically relevant interactions of Pantoprazole with other drugs with the same metabolic pathways are not expected.

Therefore, when coadministered with Pantoprazole, adjustment of the dosage of Pantoprazole or of such drugs may not be necessary]. There was also no interaction with concomitantly administered antacids. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly should be monitored for increases in INR (International Normalized Rtaio) and prothrombin time.

Concomitant use of atazanavir and proton pump inhibitors is not recommended. Co-administration of atazanavir with proton pump inhibitors is expected to substantially decrease atazanavir plasma concentrations and thereby reduce its therapeutic effect.

Because of profound and long lasting inhibition of gastric acid secretion, Pantoprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (eg, ketoconazole, ampicillin esters, and iron salts).

4.6 Pregnancy and lactation:

PANTOPRAZOLE:

US FDA Pregnancy Category B: Teratology studies have been performed in rats at oral doses up to 450 mg/kg/day (88 times the recommended human dose based on body surface area) and in rabbits at oral doses up to 40 mg/kg/day (16 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to Pantoprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

DOMPERIDONE:

US FDA's Pregnancy Category C: Either studies in animals have revealed adverse effects on the foetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available.

Drugs should be given only if the potential benefit justifies the potential risk to the foetus. Currently, there is a lack of data on the use of Domperidone in pregnant women. Hence the combination of Pantoprazole & Domperidone should only be used if the benefit outweighs the potential risk to the fetus.

Nursing Mothers:

PANTOPRAZOLE:

Pantoprazole and its metabolites are excreted in the milk of rats. Pantoprazole excretion in human milk has been detected in a study of a single nursing mother after a single 40 mg oral dose. The clinical relevance of this finding is not known. Many drugs which are excreted in human milk have a potential for serious adverse reactions in nursing infants. Based on the potential for tumorigenicity shown for Pantoprazole in rodent

carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the benefit of the drug to the mother.

4.6 Pregnancy and lactation:{CONTD}

DOMPERIDONE:

The drug is excreted in breast milk of lactating rats (mostly as metabolites: peak concentration of 40 and 800 ng/mL after oral). This probably also occurs in women. It is not known whether this is harmful to the newborn. Therefore breast-feeding is not recommended for mothers who are taking Domperidone.

Hence the combination of Pantoprazole and Domperidone is not recommended for nursing mother.

4.7 Effects on Ability to drive & Use Machines:

Pantoprazole & Domperidone combination has no or negligible influence on the ability to drive and use machines. Adverse drug reactions such as dizziness and visual disturbances may occur (see section 4.8). If affected, patients should not drive or operate machines.

4.8 ADVERSE REACTIONS:

Worldwide, more than 11,100 patients have been treated with Pantoprazole in clinical trials involving various dosages and duration of treatment. In general, Pantoprazole has been well tolerated in both short-term and long-term trials.

The following treatment-emergent events, regardless of causality, occurred at a rate of > 1% in Pantoprazole-treated patients: anxiety, arthralgia, asthenia, back pain, bronchitis, chest pain, constipation, cough increased, dizziness, dyspepsia, dyspnea, flu syndrome, gastroenteritis, gastrointestinal disorder, hyperlipemia, hypertonia, infection, liver function tests abnormal, migraine, nausea, neck pain, pain, pharyngitis, rectal disorder, rhinitis, ALT increased, sinusitis, upper respiratory tract infection, urinary frequency, urinary tract infection, and vomiting.

Domperidone has been found to be associated with increased serum prolactin, which may be associated with galactorrhea, less frequently gynaecomastia, breast enlargement and

4.8 ADVERSE REACTIONS:

soreness. Reduced libido has been reported. Occasional rashes and other allergenic phenomena are also reported. Domperidone does not readily cross the normally functioning blood brain barrier and is therefore less likely to interfere with the central dopaminergic function. However, acute extrapyramidal dystonic reactions have been reported with Domperidone.

4.9 OVERDOSAGE AND TREATMENT OF OVERDOSAGE:

PANTOPRAZOLE:

Experience in patients taking very high doses of Pantoprazole (> 240 mg) is limited. There have been spontaneous reports of overdosage with Pantoprazole, including a suicide in which Pantoprazole 560 mg and undetermined amounts of chloroquine and zopiclone were also ingested. There have also been spontaneous reports of patients taking similar amounts of Pantoprazole (400 mg and 600 mg) with no adverse effects.

Pantoprazole is not removed by hemodialysis. In case of overdosage, treatment should be symptomatic and supportive.

Single oral doses of Pantoprazole at 709 mg/kg, 798 mg/kg, and 887 mg/kg were lethal to mice, rats, and dogs, respectively. The symptoms of acute toxicity were hypoactivity, ataxia, hunched sitting, limb-splay, lateral position, segregation, absence of ear reflex, and tremor.

DOMPERIDONE:

Symptoms: Overdose has been reported primarily in infants and children. Symptoms of overdosage may include disorientation, somnolence and extrapyramidal reactions.

Treatment: There is no specific antidote to Domperidone, but in the event of overdose, the administration of activated charcoal may be useful. Anticholinergics, antiparkinson drugs may be useful in controlling extrapyramidal reactions.

The patient should be observed closely and supportive measures employed.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacotherapeutic group: Proton pump inhibitors & Propulsives(Antiemetic)

ATC code: Pantoprazole: A02BC02; Domperidone: A03F A03

Mechanism of action:

PANTOPRAZOLE:

Pantoprazole is a proton pump inhibitor (PPI) that suppresses the final step in gastric acid production by covalently binding to the (H+,K+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. This effect leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. The binding to the (H+,K+)-ATPase results in a duration of antisecretory effect that persists longer than 24 hours for all doses tested (20 mg to 120 mg).

Antisecretory Activity: Under maximal acid stimulatory conditions using pentagastrin, a dose-dependent decrease in gastric acid output occurs after a single dose of oral (20-80 mg) Pantoprazole in healthy volunteers. Pantoprazole given once daily results in increasing inhibition of gastric acid secretion.

Serum Gastrin Effects: Fasting serum gastrin levels were assessed in two double-blind studies of the acute healing of erosive esophagitis (EE) in which 682 patients with gastroesophageal reflux disease (GERD) received 10, 20, or 40 mg of Pantoprazole for up to 8 weeks. At 4 weeks of treatment there was an increase in mean gastrin levels of 7%, 35%, and 72% over pretreatment values in the 10, 20, and 40 mg treatment groups, respectively. A similar increase in serum gastrin levels was noted at the 8 week visit with mean increases of 3%, 26%, and 84% for the three Pantoprazole dose groups, respectively.

5. PHARMACOLOGICAL PROPERTIES:{CONTD}

DOMPERIDONE:

Domperidone is a unique gastro-prokinetic and antiemetic drug. It is a peripheral dopamine 2 receptor antagonist. Domperidone regulates the motility of gastric and small intestinal smooth muscle cells and has shown to have some effects on the motor function of the esophagus. It increases the duration of antral and duodenal contractions and also lower esophageal sphincter resting pressure thus stimulating gastric emptying both in the animals and in man. Domperidone is effective in relief of symptoms of reflux esophagitis.

Domperidone is a dopamine antagonist with anti-emetic properties, Domperidone does not readily cross the blood-brain barrier. In Domperidone users, especially in adults,

extrapyramidal side effects are very rare, but Domperidone promotes the release of prolactin from the pituitary. Its anti-emetic effect may be due to a combination of peripheral (gastrokinetic) effects and antagonism of dopamine receptors in the chemoreceptor trigger zone, which lies outside the blood-brain barrier in the area postrema. Animal studies, together with the low concentrations found in the brain, indicate a predominantly peripheral effect of Domperidone on dopamine receptors. Studies in man have shown oral Domperidone to increase lower oesophaegeal pressure, improve antroduodenal motility and accelerate gastric emptying. There is no effect on gastric secretion.

5.2 Pharmacokinetic properties:

PANTOPRAZOLE:

Absorption: The absorption of Pantoprazole is rapid, with a Cmax of 2.5 µg/mL that occurs approximately 2.5 hours after administration of single or multiple 40 mg doses of Pantoprazole. Pantoprazole is well absorbed; it undergoes little first-pass metabolism resulting in an absolute bioavailability of approximately 77%. Pantoprazole absorption is not affected by concomitant administration of antacids.

5. PHARMACOLOGICAL PROPERTIES:{CONTD}

5.2 Pharmacokinetic properties: [CONTD]

Distribution: The apparent volume of distribution of Pantoprazole is approximately 11.0-23.6 L, distributing mainly in extracellular fluid. The serum protein binding of Pantoprazole is about 98%, primarily to albumin.

Metabolism: Pantoprazole is extensively metabolized in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the Pantoprazole metabolites have significant pharmacologic activity. [CYP2C19 displays a known genetic polymorphism due to its deficiency in some sub-populations (eg, 3% of Caucasians and African-Americans and 17%-23% of Asians are poor metabolisers). Although these sub-populations of slow

Pantoprazole metabolizers have elimination half-life values of 3.5 to 10.0 hours in adults, they still have minimal accumulation (< 23%) with once daily dosing].

Elimination: After a single oral or intravenous dose of 14C-labeled Pantoprazole to healthy, normal metabolizer volunteers, approximately 71% of the dose was excreted in the urine with 18% excreted in the feces through biliary excretion. There was no renal excretion of unchanged Pantoprazole.

DOMPERIDONE:

Absorption: In fasting subjects, Domperidone is rapidly absorbed after oral administration, with peak plasma concentrations at 30 to 60 minutes. The low absolute bioavailability of oral Domperidone (approximately 15%) is due to an extensive first-pass metabolism in the gut wall and liver. Although Domperidone's bioavailability is enhanced in normal subjects when taken after a meal, patients with gastro-intestinal complaints should take Domperidone 15-30 minutes before a meal. Reduced gastric acidity impairs the absorption of Domperidone. Oral bioavailability is decreased by prior concomitant administration of cimetidine and sodium bicarbonate. The time of peak absorption is slightly delayed and the AUC somewhat increased when the oral drug is taken after a meal.

5. PHARMACOLOGICAL PROPERTIES:

5.2 Pharmacokinetic properties:

Distribution: Oral Domperidone does not appear to accumulate or induce its own metabolism; a peak plasma level after 90 minutes of 21 ng/ml after two weeks oral administration of 30 mg per day was almost the same as that of 18 ng/ml after the first dose. Domperidone is 91-93% bound to plasma proteins. Distribution studies with radiolabelled drug in animals have shown wide tissue distribution, but low brain concentration. Small amounts of drug cross the placenta in rats.

Metabolism: Domperidone undergoes rapid and extensive hepatic metabolism by hydroxylation and N-dealkylation. In vitro metabolism experiments with diagnostic inhibitors revealed that CYP3A4 is a major form of cytochrome P-450 involved in the N-dealkylation of Domperidone, whereas CYP3A4, CYP1A2 and CYP2E1 are involved in Domperidone aromatic hydroxylation.

Excretion: Urinary and faecal excretions amount to 31 and 66% of the oral dose respectively. The proportion of the drug excreted unchanged is small (10% of faecal

excretion and approximately 1% of urinary excretion). The plasma half-life after a single oral dose is 7-9 hours in healthy subjects but is prolonged in patients with severe renal insufficiency.

5.3 Preclinical safety data:

Preclinical data reveal no special hazard to humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Starch(Maize),Lactose, Croscarmellose Sodium, Povidone K-30{PVPK-30}, Purified Water, Talc {Purified Talcum}, Magnesium Stearate & Colloidal Silicon Dioxide.

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life: 24 MONTHS.

6.4 Special precautions for storage:

Store at a temperature not exceeding 30 °C.

KEEP OUT OF REACH OF CHILDREN.

PROTECT FROM MOISTURE AND LIGHT.

6.5 Nature and contents of container:

Plain/Printed Aluminium foil with LDPE layer. Strip pack of 10 tablets.

Secondary pack: 3 x 10's

6.6 Special precautions for disposal and other handling:

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER:

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8. MA number issued by Ethiopian FDA:

04661/4447/NMR/2017

9. Date of first authorization/renewal of the authorization:

25-07-2021

10. DATE OF REVISION OF THE TEXT:

04-07-2023